EXHIBIT 8

WARNING LETTER

Torrent Pharmaceuticals Limited

MARCS-CMS 585255 — OCTOBER 08, 2019

Delivery Method:

VIA UPS

Reference #:

320-20-03

Product:

Drugs

Recipient:

Mr. Samir Mehta

CEO

Torrent Pharmaceuticals Limited

Torrent House
Off. Ashram Road
Ahmedabad 380009 Gujarat
India

Issuing Office:

Center for Drug Evaluation and Research

10903 New Hampshire Avenue
Silver Spring, MD 20993
United States

Warning Letter 320-20-03

October 8, 2019

Dear Mr. Mehta:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Torrent Pharmaceuticals Limited, FEI 3005029956, at Ahmedabad-Mehsana Highway, Taluka-Kadi, Indrad, Gujarat from April 8 to 16, 2019.

This warning letter summarizes significant violations of current good manufacturing practice (CGMP) regulations for finished pharmaceuticals. See 21 CFR, parts 210 and 211.

Because your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to CGMP, your drug products are adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 351(a)(2)(B).

We reviewed your May 7, 2019, response to our Form FDA 483 in detail and acknowledge receipt of your subsequent correspondence.

During our inspection, our investigators observed specific violations and deviations including, but not limited to, the following.

1. Your firm failed to follow written procedures for production and process control designed to assure that the drug products you manufacture have the identity, strength, quality, and purity they purport or are represented to possess (21 CFR 211.100(b)).

Your firm did not appropriately follow your written and approved process validation (PV) protocol which required quality attributes to be met for "three consecutive" batches to qualify an alternate active pharmaceutical ingredient (API). Several PV batches using a new alternate API were manufactured for Losartan Potassium Tablets USP 50 mg and USP 100 mg without appropriately following your protocol.

Specifically, after the first of the three PV batches failed for dissolution, assay, and **(b)(4)**, your firm added a fourth batch which was outside of your written protocol. However, the fourth batch also failed specifications for dissolution. Multiple out-of-specification (OOS) investigations were initiated and quality rejected all four PV batches.

You developed a new interim protocol to justify commercial use of the alternate API and circumvented your original protocol, even though you had data demonstrating your process was not capable of producing quality material using the new alternate API. Numerous Losartan Potassium Tablets USP 50 mg and USP 100 mg commercial batches were manufactured with this new alternate API and released to the U.S. market despite the PV failures. In addition, multiple batches of Losartan Potassium were recalled for unacceptable amounts of nitrosamine impurities.

Your response acknowledged that you did not follow your written and approved validation protocols. You also stated the change in API had no impact on the manufacturing process and the quality of the finished drug. Your response is inadequate. You failed to provide adequate root cause for the initial PV batches failures. You also failed to provide adequate justification in your process validation protocols to support approval of the alternate API with known PV failures.

Process validation evaluates the soundness of design and state of control of a process throughout its lifecycle. Each significant stage of a manufacturing process must be designed appropriately and assure the quality of raw material inputs, in-process materials, and finished drugs. Process qualification studies determine whether an initial state of control has been established.

Successful process qualification studies are necessary before commercial distribution of drugs. Thereafter, ongoing vigilant oversight of process performance and product quality is necessary to ensure you maintain a stable manufacturing operation throughout the product lifecycle.

In response to this letter, provide:

- A detailed summary of your validation program for ensuring a state of control throughout the product lifecycle, along with associated procedures. Describe your program for process performance qualification and ongoing

monitoring of both intra-batch and inter-batch variation to ensure a continuing state of control.

- A timeline for performing appropriate process performance qualification (PPQ) for each of your marketed drug products.
- A review of all data that supports your process validation for commercially distributed drug products.

See FDA's guidance document *Process Validation: General Principles and Practices* for general principles and approaches that FDA considers appropriate elements of process validation at https://www.fda.gov/media/71021/download (https://www.fda.gov/media/71021/download).

2. Your firm failed to thoroughly investigate any unexplained discrepancy or failure of a batch or any of its components to meet any of its specifications, whether or not the batch has already been distributed (21 CFR 211.192).

Your investigations into OOS testing results were inadequate. Multiple OOS investigations related to assay, **(b)(4)**, and dissolution were closed without assignable root cause, or lacked adequate scientific justification for root cause. Despite the inadequate OOS investigations, your firm disregarded initial failing OOS results and released batches based on retested results.

For example, OOS investigation OOS/IN/F/FP/17/238 for Losartan Potassium and Hydrochlorothiazide (HCTZ) Tablet **(b)(4)** for batch number BP02D026 was initiated on July 4, 2017, due to a high HCTZ assay value. The result was super potent, **(b)(4)**%, versus a **(b)(4)**–**(b)(4)**% specification. This OOS result was confirmed during your phase I laboratory investigation without establishing a root cause. During your phase II investigation, neither a manufacturing nor laboratory error was conclusively identified. Despite no assignable root cause, the initial high OOS results were invalidated and the **(b)(4)** was released based on retested reserve sample results. The resulting finished product batch was distributed to the U.S. market.

Multiple examples of improperly invalidating initial failing OOS results were also observed in other drug products. In addition, your firm has a high percentage rate (60–70%) for invalidated initial OOS test results between January 2017 and March 2019.

Your response indicated your awareness of a high percentage rate of invalidated OOS test results without appropriate investigation. You stated that between January 2017 to March 2019, you have a downward trend from 77% to 41%. Major contributors are human error, instrument/column error, and method error. Your response is inadequate. You failed to provide a retrospective review of all your drug products to determine if you are attributing root cause appropriately, reporting OOS results correctly, and implementing adequate corrective and preventive actions (CAPA).

This is a repeat observation from FDA's April 17–28, 2017, inspection at your Indrad facility. The FDA also cited a similar CGMP observation for inadequate investigations at your Torrent Pharmaceuticals Limited Dahej facility (FEI 3010228235) in Gujarat during a March 11–19, 2019, inspection.

Repeated failures at multiple sites demonstrate that executive management oversight and control over the manufacture of drugs is inadequate.

Your executive management remains responsible for fully resolving all deficiencies and ensuring ongoing CGMP compliance. You should immediately and comprehensively assess your company's global manufacturing operations to ensure that systems, processes, and the products manufactured conform to FDA requirements.

In response to this letter, provide:

- A retrospective, third-party review of all invalidated OOS (including in-process and release/stability testing) results for products currently in the U.S. market and within expiry as of the date of this letter, and a report summarizing the findings of the analysis, including the following for each OOS:

  - Determine whether the scientific justification and evidence relating to the invalidated OOS result conclusively or inconclusively demonstrates causative laboratory error.
  - For investigations that conclusively establish laboratory root cause, provide rationale and ensure that all other laboratory methods vulnerable to the same or similar root cause are identified for remediation.
  - For all OOS results found by the retrospective review to have inconclusive or no root causes identified in the laboratory, include a thorough review of production (e.g., batch manufacturing records, adequacy of the manufacturing steps, suitability of equipment/facilities, variability of raw materials, process capability, deviation history, complaint history, batch failure history). Summarize potential manufacturing root causes for each investigation, and any manufacturing operation improvements.
  - A comprehensive review and remediation plan for your OOS result investigation systems. The CAPA should include but not be limited to the following:
    - Quality unit oversight of laboratory investigations.
    - Identification of adverse laboratory control trends.
    - Resolution of causes of laboratory variation.
    - Initiation of thorough investigations of potential manufacturing causes whenever a laboratory cause cannot be conclusively identified.
    - Adequately scoping of each investigation and its CAPA.
    - Revised OOS investigation procedures with these and other remediations.

For more information about handling failing, out-of-specification, out-of-trend, or other unexpected results and documentation of your investigations, see FDA's guidance document *Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production* at https://www.fda.gov/media/71001/download (https://www.fda.gov/media/71001/download).

CGMP Consultant Recommended

We acknowledge that you have hired a consultant. Because of your compliance history with inadequate investigations, we recommend that any consultant you engage is qualified as set forth in 21 CFR 211.34 to assist your firm in meeting CGMP requirements. After your consultant's audit, provide a summary of the report.

Your use of a consultant does not relieve your firm's obligation to comply with CGMP. Your firm's executive management remains responsible for resolving all deficiencies and systemic flaws to ensure ongoing CGMP compliance.

Conclusion

The violations cited in this letter are not intended to be an all-inclusive list of violations that exist at your facility/in connection with your products. You are responsible for investigating and determining the causes of these violations and for preventing their recurrence or the occurrence of other violations.

If you are considering an action that is likely to lead to a disruption in the supply of drugs produced at your facility, FDA requests that you contact CDER's Drug Shortages Staff immediately, at drugshortages@fda.hhs.gov, so that FDA can work with you on the most effective way to bring your operations into compliance with the law. Contacting the Drug Shortages Staff also allows you to meet any obligations you may have to report discontinuances or interruptions in your drug manufacture under 21 U.S.C. 356C(b). This also allows FDA to consider, as soon as possible, what actions, if any, may be needed to avoid shortages and protect the health of patients who depend on your products.

Until you correct all violations completely and we confirm your compliance with CGMP, FDA may withhold approval of any new drug applications or supplements listing your firm as a drug manufacturer.

Failure to correct these violations may also result in the FDA refusing admission of articles manufactured at Torrent Pharmaceuticals Limited, Ahmedabad-Mehsana Highway, Taluka-Kadi, Indrad, Gujarat, into the United States under section 801(a)(3) of the FD&C Act, 21 U.S.C. 381(a)(3). Articles under this authority may be subject to refusal of admission, in that the methods and controls used in their manufacture do not appear to conform to CGMP within the meaning of section 501(a)(2)(B) of the FD&C Act, 21 U.S.C. 351(a)(2)(B).

After you receive this letter, respond to this office in writing within 15 working days. Specify what you have done since our inspection to correct your violations and to prevent their recurrence. If you cannot complete corrective actions within 15 working days, state your reasons for delay and your schedule for completion.

Send your electronic reply to CDER-OC-OMQ-Communications@fda.hhs.gov (mailto:CDER-OC-OMQ-Communications@fda.hhs.gov) or mail your reply to:

Towanda Terrell

Compliance Officer

U.S. Food and Drug Administration

White Oak Building 51, Room 4235

10903 New Hampshire Avenue

Silver Spring, MD 20993

USA

Please identify your response with FEI 3005029956.

Sincerely,

/S/

Francis Godwin

Director

Office of Manufacturing Quality

Office of Compliance

Center for Drug Evaluation and Research

CC: Mr. Ashish Hajarnis

Vice President (Works)

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